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Syndromics: A Bioinformatics Approach for Neurotrauma Research

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Abstract Substantial scientific progress has been made in the past 50 years in delineating many of the biological mechanisms involved in the primary and secondary injuries following trauma to the spinal cord and brain. These advances have highlighted numerous potential therapeutic approaches that may help restore function after injury. Despite these advances, bench-to-bedside translation has remained elusive. Translational testing of novel therapies requires standardized measures of function for comparison across different laboratories, paradigms, and species. Although numerous functional assessments have been developed in animal models, it remains unclear how to best integrate this information to describe the complete translational "syndrome" produced by neurotrauma. The present paper describes a multivariate statistical framework for integrating diverse neurotrauma data and reviews the few papers to date that have taken an information-intensive approach for basic neurotrauma research. We argue that these papers can be described as the seminal works of a new field that we call "syndromics", which aim to apply informatics tools to disease models to characterize the full set of mechanistic inter-relationships from multi-scale data. In the future, centralized databases of raw neurotrauma data will enable better syndromic approaches and aid future translational research, leading to more efficient testing regimens and more clinically relevant findings.

Keywords Spinal cord injury · Traumatic brain injury · Multivariate statistics · Outcome measures · Assessment

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Introduction

Basic research on spinal cord injury (SCI) and traumatic brain injury (TBI) has sought to tackle the complex biological milieu produced by trauma and reduce it down to its fundamental mechanistic processes for therapeutic targeting. Over the past 50 years, this approach has uncovered numerous biological mechanisms contributing to dysfunction, including oxidative-stress (1–3), apoptotic cell death (4, 5), tissue loss (6, 7), neuroinflammation (8–11), alterations in organization and plasticity (12–16), and long-term changes in function (17–25), among others. This intensive effort has provided a wealth of knowledge about individual patho-biological mechanisms; however, translation of this knowledge into human therapeutics has remained elusive (26–30). Large-scale integration of diverse mechanistic findings has the potential to aid in translation by characterizing the complex constellation (i.e., the "syndrome") of biological and functional changes after trauma. Syndrome-detection from diverse sources of raw data requires the application of computationally intensive integrative approaches that are, at the present time, uncommon in the basic neurotrauma literature. The current paper reviews the diverse biological and functional measures that have been characterized for both SCI and TBI, providing a data-rich framework from which syndrome-level analyses can be built. We then review the few recent studies that have used systems biology approaches to integrate diverse neurotrauma data. We argue that these papers can be viewed as the seminal works of a new field that we call "syndromics" which aims to understand complex disease states as integrated and well-characterized syndromes that can be quantified through the use of bioinformatics approaches (Fig. 1). This approach borrows from methods currently used in epidemiology known as "syndromic surveillance" to monitor and predict

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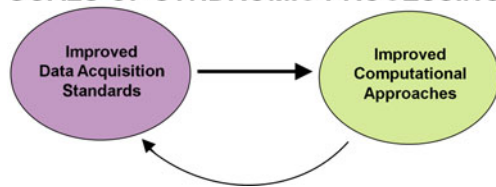
Fig. 1 Iterative relationship between data acquisition and computational results

disease outbreaks by integrating diverse sources of information (31). We use the term syndromics to refer to a similar paradigm applied to preclinical, mechanistic studies with the goal of providing a translational bridge between the clinical and preclinical literature. The term syndromics is also reminiscent of other computational biology frameworks such as "genomics" and "proteomics", involving the integration of diverse genetic and protein expression information, respectively. The statistical methods used in syndromics are very similar to these other "omics"; however the data analyzed tend to be more multi-scalar in nature.

A fundamental premise of syndromics is that it is possible to integrate diverse measures from multiple biological and functional assays into a unified snapshot of the state of the affected individual. In the following review, we first discuss some of the pathological and functional consequences observed following neurotrauma, and the outcome measures used to assess them. We then review some of the statistical techniques that could be applied to neurotrauma data for syndromic integration of these multiple outcomes. Most of the preclinical examples come from SCI; however, syndromics is a general framework that can be applied to TBI, stroke, and other disease models as well.

One Traumatic Event, Multiple Interrelated Biological Effects

Traumatic injury to the central nervous system (CNS) produces complex biological sequelae. For example, SCI alters expression of a wide range of genomic and proteomic markers (32–37). These complex molecular events are involved in a cascade of biological changes, including cell damage through excitoxicity and lipid peroxidation, resulting in cell death through necrosis and apoptosis (4, 38–44). Each of these cell-death responses has a variety of telltale markers. For example, excitotoxicity is associated with cytoplasmic swelling (45, 46), increased calcium (Ca^{2+}) influx (47, 48), alterations in glutamate receptors (41, 49, 50), changes in membrane permeability (51, 52), and acute electrophysiological changes (53–55). Apoptosis has been measured through distinctive morphological changes such

as nuclear fragmentation and chromatin condensation (4, 56) or through a variety of cell signaling markers including positive labeling for TUNEL, caspases, fluorojade-B, and others (4, 57–62).

Cell death and compensatory repair occur in a dynamically changing tissue microenvironment that includes changes in inflammatory cytokine levels, altered inflammatory states in CNS microglia, and waves of CNS infiltration by circulating immune cells (9, 63–67). This neuroinflammation has been implicated in cell death and secondary injury (41, 68–74) as well as neuroprotection and repair (75–78). This speaks to the complexity of the interrelationships between different biological mechanisms and highlights the difficulty with predicting outcome using only one or two isolated biomarkers (79–82). The emergent relationships among multiple measures could help define the conditions under which a particular simple relationship prevails over another. For example, proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) are released following trauma to the nervous system (83, 84) and can either have detrimental effects such as contributing to neural cell death (41, 85), or can serve a neuroprotective function (86–88), depending on the context. However, the specific factors dictating TNFα function are not well understood, and different conclusions can be made by monitoring different aspects of TNF signaling. The failure to account for complex, multi-inflected interactions among outcomes reduces replicability of findings and leads to controversies that could be resolved by including a more complete set of measures, reflecting a more complete set of biological mechanisms.

Like cell-death measurements, histological sparing after neurotrauma is often quantified using multiple different measurements. For example in the SCI literature, common morphometric measurements include cross-sectional gray matter sparing, white matter sparing, and lesion area and volume (6, 89–93). In addition, it is common for researchers to use more specific immunohistochemical markers to measure specific cellular and subcellular changes (4, 5, 66, 67, 94, 95). For example, changes in oligodendrocyte precursor cell proliferation/differentiation have been measured as harbingers of white matter sparing and remyelination (96–102). Motor neuron sparing can be quantified as an assay of functional gray matter sparing (41). Reactive astrocytes have been measured with a specific focus on their relationship to the glial scar (103–105). Microglia/monocyte numbers and activity state have been quantified to characterize their relationship to other morphological changes (106–109).

This litany of changes, ranging from subcellular to histological, is thought to have implications for not only cell death but also compensatory plasticity after neurotrauma. To measure morphological plasticity such as

regeneration and sprouting, anterograde tracers have been used to target specific tracts of interest such as the corticospinal tract (CST) (16, 110–114), rubrospinal tract (115, 116), and motor unit organization (117, 118), among others. The relationship between these regenerative changes and other histological changes such as growth factor levels (119–121) and breakdown of the glial scar (122, 123) are thought to predict the degree of axonal regrowth across the lesion and provide a substrate for functional recovery (110, 122–124).

In addition to regeneration across the lesion, there is substantial plasticity and reorganization at sites remote to a focal neurotrauma. For example, in the SCI literature, it has been well established that there is plasticity and functional reorganization below a complete transection (117, 124–131). With training, the spinal cord is capable of learning a variety of motor tasks, including Pavlovian associations (132–136), instrumental learning (129, 131, 137–141) and stepping on a treadmill (124, 125, 142–146). This capacity for use-dependent plasticity in the spinal cord has been shown to rely upon propriospinal tract relays (124) and glutamate receptor-mediated plasticity in the lumbar cord (147, 148). There is also substantial reorganization in the cortex following SCI (149–157), which appears to be largely mediated by the extent of use of the relative areas represented in the cortex and compensation from the surrounding representations occurs to promote functional recovery.

Recovery after injury is likely to result from a complex amalgamation of all of these tissue changes working in concert to generate the functional state of the affected individual. Detecting systematic patterns from this complexity is a daunting task, however, advanced computational approaches have been effectively used to deal with similar levels of complexity in other fields, including information systems (158), physics (159, 160), meteorology (161), economics (162), epidemiology (163–165), psychology (166), chemometrics (167, 168), genomics (169–173), and proteomics (174). The general approach for these fields has been to build vast data repositories that allow integration of multiple pieces of information using multivariate statistics. By taking a similar approach to neurotrauma, syndromics provides an opportunity to leverage state-of-the art knowledge about multiple biological mechanisms to predict functional recovery (16) and compare findings across species (175, 176).

One Traumatic Event, Multiple Functional Consequences

Functional changes are a hallmark of neurotrauma and are the major target for treatment of affected patients (177). SCI is associated with a wide range of functional disturbances including pathological pain and other sensory changes, loss of sexual function, bladder and bowel changes, and motor impairments (for review see (178)). Biological mechanisms are important for therapeutic development, yet the ultimate goal is to affect function. Therefore, it is critical to understand precisely what we are measuring when we take functional measures after neurotrauma. Ultimately, this issue falls within the field of psychometrics, the scientific discipline concerned with neurobehavioral scale development and metric validation (179, 180). Psychometrics is a vast literature (181–183) that provides standards for assessing reliability and validity of a given scale. This field that has given rise to many of the tools used for clinical neurological assessment after neurotrauma, such as neuropsychological testing batteries (184–186), personality inventories (187), PTSD measures (188), quality-of-life indices (189–191), and functional independence measures (192–197). Many of the basic principles from this scientific discipline, such as guidelines for reliability and validity assessment, have been applied in the clinical neurotrauma literature (197–210). However, the basic research community in neurotrauma has been less attentive to the scale development concerns (for exceptions see (211–214)), and metric properties studies are largely lacking (215).

Despite the lack of clarity about reliability and validity testing for many of the current scales, over the last 50 years, the basic SCI literature has produced numerous measures to assess injury at a behavioral level (16, 25, 157, 211–214, 216–236). A full summary of most of these methods is beyond the scope of the present paper and have been reviewed in detail elsewhere (237–244). Some of the most popular measures have been open-field locomotor assessments (211, 212, 217, 230, 231), footprint analysis (218, 232–234, 245), and fine-grained physiological outcomes such as electromyography (EMG) and kinematics (222, 234–236, 246–249). Additional functional assessments have included the inclined plane test, and various methods for assessing contact placing responses and foot-placement such as gridwalk test, beam walk, and the horizontal ladder (25, 89, 92, 241, 250–252).

There is little consensus about what is the most appropriate or "best" measure of outcome after experimental neurotrauma. It is therefore common for researchers to perform a battery of functional assessments in the context of therapeutic testing (241). Since there are no clear rules for determining which subsets of outcomes should be reported in published work, researchers often report only a subset of the collected data in a given publication to highlight statistically significant effects and to achieve clarity of presentation. This opens the possibility that researchers can repeatedly test their hypothesis on multiple outcomes and then make strong conclusions on a minority

of outcomes that show significant effects. Such an approach increases the risk of a type I error (reporting a significant effect when there is not one). This is perhaps highlighted by the recent high-profile studies in which researchers have been unable to replicate each other's work in the preclinical setting (253–257). On the other hand, it is possible that different functional measures reflect different components of the complex, multifaceted syndrome that follows SCI. It is possible, for example, that animals could perform well on a test of open field locomotion, but still lack some of the modulatory sensory or reflex function that is necessary for locomotion in a complex environment with obstacles and variations in surface texture (258). Conversely, rearrangement of the somatosensory cortex following SCI suggests that an animal could perform well on tests of sensory function but lack the lower motor neuron control necessary for open-field locomotion (150). Thus, there is a need for comprehensive scales that capture all of the subcomponents involved in normal function, producing global, syndrome scores that reflect the entire functional state of the animal.

In an attempt to address this issue, some researchers have used integrative scales or testing batteries that combine elements of several of the scales discussed in previous sections (216, 241, 259). For example, in the follow-up paper to the 1954 publication of his influential locomotor scale, Tarlov reported that there were different time courses for recovery of tactile nociception (pin-prick) and locomotion, providing a window into the complex interactions between sensory and motor function (217, 259). In keeping with this tradition, Gale et al. (1985) incorporated sensory function as well as multiple motor indices in their complex test, the combined behavioral score (CBS). The CBS consists of eight subtests that were designed to tap into locomotion, proprioception, cutaneous reflexes, posture, and nociceptive processing. The raw scores from these subtests are converted to reverse-weighted CBS subscores and then added to yield a scale that ranges from 0 (no dysfunction) to 100 (complete dysfunction). Therefore, the global CBS can be interpreted as a percent dysfunction (216).

Following the initial development of the CBS, several papers came out suggesting that it was highly correlated with less extensive outcomes such as the five-point Tarlov open-field scores and the inclined plane test (260–263). Some reports suggested that exclusion of some of the subtests on the CBS reduces extraneous variability, resulting in greater validity with regard to lesion size (264). In 1995, a modified version of the Tarlov scale was produced by Basso, Beattie, and Bresnahan (BBB) (211) that was subjected to careful reliability (265) and validity testing (211, 265) as part of the multicenter animal SCI study (MASCIS) (266). The BBB was released with well-designed, easy-to-use scoring sheets and training materials.

Subsequent work revealed that multiple other measurement techniques did not provide substantial gains in useful information over the BBB (241), and the field adopted this easy-to-use locomotor outcome as the de facto standard for functional assessment in rodent SCI models, garnering over 1,100 citations since its release in 1995 (267). Subsequent modifications have been made to this scale, including one specifically for use in mouse models (212), one utilizing a straight ally testing field (230), and one that uses a computer program to assist with recording and scoring (268).

It has been pointed out that there is often an inverse relationship between ease-of-use of a scale and its precision (237). On one end of the spectrum, there are simple-to-use, but error-prone scales like the five-point Tarlov (217), which describes function using ambiguous terms such as "good movement of the joints" (score = 2) and "complete recovery" (score = 4). On the other end of the spectrum are high-resolution kinematic measures using high-speed, high-definition cameras, and precision placement of joint markers with SMPTE timestamps for data alignment with electrophysiological outputs (224, 247, 269–272). The former may lack the precision necessary to detect incremental functional improvement whereas the latter produces high-precision, but at a cost in money, analysis time, and expertise required (237). The BBB scale attempts to strike a balance between these two extremes by providing strict operational definitions intended to guide observational scoring and increase reliability (265). However, the BBB has been criticized for its insensitivity in the extreme lower and upper portions of the scale where incremental improvements in function may not be accurately represented as incremental improvement in score (215, 273). For example, inter-limb coordination as measured by the upper end of the BBB scale shows some statistical wobble (215) and does not always correlate with results from detailed analysis of stepping patterns using automated footprint analysis (245, 273), kinematics (274), or robotic gait analysis (275). A fundamental issue that arises from these comparisons is: "What are the best measures of function?" The answer to this question is not always clear, and in many cases, it can be countered with another question: "Better for what purpose?", as some measures may be better at detecting functional changes due to a particular therapeutic target. Instead of choosing between BBB, kinematics, and EMG in hopes of choosing the best one, it is possible to include all measurements to gain better resolution of the underlying syndrome. One benefit of a syndromics approach is that it incorporates information from all measures and circumvents arbitrary decisions about which outcomes reflect the "best measures" for therapeutic testing (see section "Statistical Pattern Detection: Coherent Patterns from Numerous Measurements").

Multiple Measurement Techniques for the Same Feature

The problem of determining the best measures is not limited to the relatively abstract concept of functional recovery. Even in the case of concrete concepts such as tissue sparing, there is little consensus on how to best quantify changes. There have been a variety of approaches taken for histopathological quantification (38, 90, 259, 264, 276–284). In the older literature, histological analyses of SCI consisted of qualitative descriptions of "typical" cords from each experimental condition (259). In more recent studies, researchers have developed ways to quantify tissue loss; however, the methods for quantification are somewhat variable across studies. The general approach in SCI is to measure the amount of gray and/or white matter sparing at the site of injury (92). Some researchers have estimated the lesion epicenter by taking serial sections and identifying the section with the largest extent of lesion and then analyzing a single coronal section to represent the lesion extent (211). Using image analysis, the area of spared gray and white matter in this slice can be calculated and then compared across experimental groups. Others have estimated lesion volume by interpolating the volume between two slices from a fixed interval (92, 264). For example, Bresnahan et al. (1987) measured the area of five sections between the rostral and caudal ends of the lesion site. The volume between these sections was calculated as the frustum of a cone, with the two sections representing the two bases of the cone. Others have quantified tissue volume in multiple ways. For example, von Euler et al. (1996) quantified tissue loss in three ways: (1) designing an ordinal scale to describe the extent of tissue loss, (2) by assuming that the lesion volume is approximately shaped like two cones with adjacent bases, and (3) by using image analysis software to reconstruct the lesion site section by section. Although one would expect the image analysis method to be the most accurate, the other two methods correlated quite highly with the section by section reconstruction ($r=0.93$ and $r=0.96$ for the ordinal and conical estimates, respectively). These high correlations imply that, although there is variability across lesion quantification techniques, different techniques may largely explain the same variance in tissue loss. Therefore, researchers can, in many cases, use an easy but primitive estimate of tissue sparing (such as the conical method) to assess tissue loss after SCI.

Others have quantified tissue using unbiased stereology (285). Stereology involves estimating tissue length, volume, area, and cell or fiber counts from sub-sampled sections to accurately reconstruct entire regions of the nervous system. Tissue volume can be determined using the Cavalieri method (277, 286, 287), which, when combined with systematic random sampling and optical or physical dissector met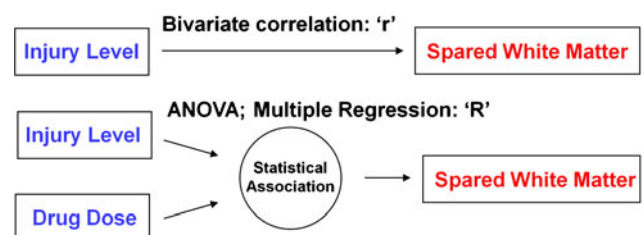hods (288, 291), can produce a fairly accurate representation of total cell and/or fiber counts within a volume of tissue (286, 288–290). This allows us to test specific hypotheses about trauma-induced alterations in specific population of cells, fiber sparing, and regeneration. These same techniques can be applied to estimate cell volume using the nucleator method, which uses radial points from the center of a pre-defined focal point (e.g., nucleolus within a cell), to the perimeter of the particle (e.g., membrane), to give an estimation of particle size (292). Additionally, myelin thickness can be determined by direct orthogonal measurements in uniform, random locations (293). These methods of stereological tissue analysis have proven very useful for SCI researchers to show cutting-edge work regarding immune response (9, 294), neuronal survival (295, 296), and plasticity (16, 297). However, given the number of alternative quantification approaches, it remains unclear which histological approaches are best for predicting functional performance, and there is a need for integrative comparisons of these various measurement methods.

Statistical Pattern Detection: Coherent Patterns from Numerous Measurements

Determining the best way to integrate information from multiple measurements represents a major challenge for translational testing. The goal of basic research is to develop outcomes that are, at once, sensitive to mechanistic therapeutics and translatable to human disease features (298). Application of the appropriate statistical tools is critical for data integration. A variety of statistical tools have been used to analyze neurotrauma data. Statistical approaches can be generally divided into *univariate* approaches and *multivariate* approaches (Fig. 2). Univariate
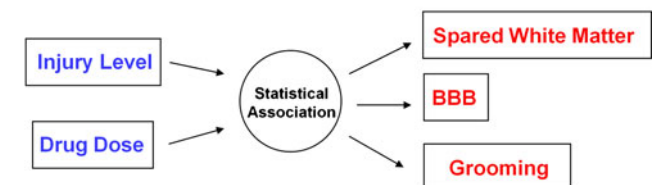

Fig. 2 Categories of statistical methods

approaches focus on how a single variable changes as a function of either: (1) a therapeutic treatment, or (2) as a correlate of one or more predictor variables. Multivariate approaches, on the other hand, monitor changes in multiple variables at once, simultaneously measuring both individual outcomes as well as the inter-relationship among the outcomes. In this way, multivariate approaches are uniquely sensitive to therapeutic approaches that simultaneously affect multiple outcomes.

As highlighted in the preceding sections, neurotrauma research often involves multiple outcomes. The historical approach for dealing with this complexity has been to use univariate statistics to assess bivariate correlations among individual outcomes or to separately test a single hypothesis on multiple individual variables and report significance when it occurs (Fig. 3). Examples of common univariate methodologies include *t* tests and analysis of variance, and bivariate correlational analysis wherein a single measure is correlated with another measure, and then this process is repeated iteratively for all outcomes (6, 151, 299). Univariate approaches have been used in validation for many of the functional assessment techniques discussed above. The "gold standard" for validity testing has been to show that a functional measure correlates with tissue loss and/or intensity of experimental trauma. As a consequence, by design many of the functional measures do infer underlying tissue loss with reasonable reliability (6, 151, 263, 299–301).

However, because there is some variability in the way that tissue loss is quantified (see section "Multiple Measurements for the Same Feature"), the validation procedures across different scales may not be comparable.

For example, the BBB scale was validated by testing whether the scale could predict the degree of experimental trauma (i.e., the degree of cord displacement or weight drop height). In addition, the scores were regressed onto the percentage of tissue sparing at the lesion epicenter (211). Other validation procedures that have used multiple quantification methodologies have found that histological quantification methods can influence conclusions about the validity of a scale (92, 264). Bresnahan et al. (1987) found that lesion area at the epicenter correlated better with three common functional measures (open-field locomotion, the inclined plane, and gridwalk) than lesion volume estimation (92). In contrast, von Euler et al. (1996) found that area of tissue loss at the lesion epicenter correlated less well with several functional measures than an ordinal lesion volume score (264). These findings illustrate the potential danger of drawing conclusions about the validity of a functional measure based on a unitary tissue quantification method. However, many functional measures do appear to reflect tissue changes in one form or another, suggesting that there is an underlying multi-dimensional disease state that is reflected across different quantification methods. Yet, univariate analyses are blind to consistent patterns among several outcomes (16, 302).

Multivariate statistical approaches represent a powerful alternative to univariate testing of neurotrauma data. Because multivariate approaches are sensitive to associations among multiple outcomes, they have the potential to identify underlying disease states that are unconstrained by the limitations of individual measures. This feature allows researchers to partition out the error that is particular to each outcome measure and to focus on the consistent disease
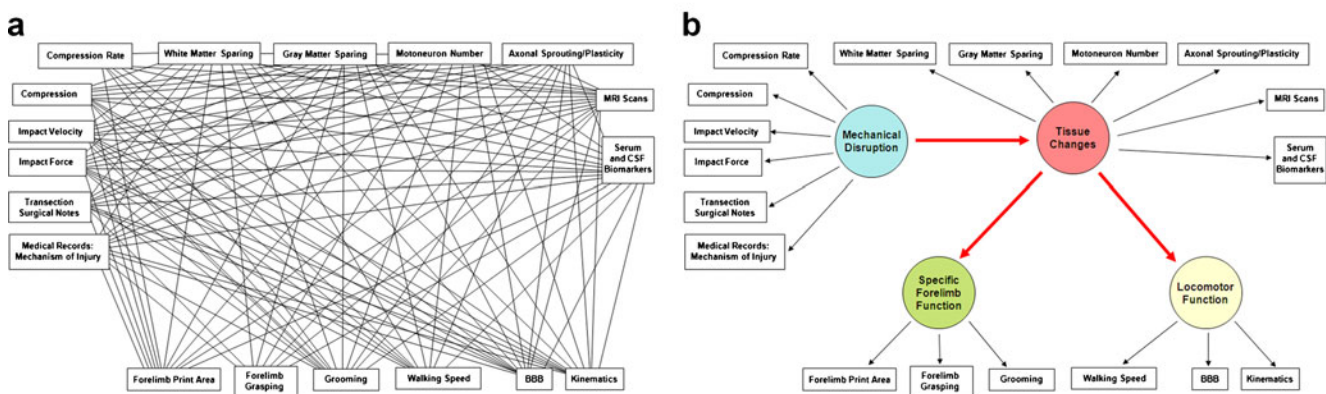
Fig. 3 Correlation distillation as a syndromic framework. The goal of syndromic analysis is to convert **a** low-level univariate statistical relationships (*lines*) among observed variables (*boxes*) into **b** a multivariate view of the underlying syndromic states (*circles*). The multivariate representation in **b**, known as a path diagram, is consistent with the conventions of structural equation modeling where directional *arrows* are used to indicate cause-and-effect relationships.

From this perspective, underlying syndrome states are conceptualized as the cause of observed outcomes, and multivariate outcome monitoring provides a more accurate window into the underlying syndrome. With more measures, the picture of the underlying syndrome becomes more clear and less distorted by the error in individual measures

patterns that are shared across outcomes (303). This produces a dramatic increase in statistical power and helps identify robust disease patterns that are less likely to be idiosyncratic to a specific outcome measure (304). At the same time, multivariate approaches can be used to identify different classes of outcomes, which can be particularly beneficial for diagnosis and treatment in clinical neurotrauma (305, 306).

To date, only a small number of papers have applied multivariate approaches to basic research in SCI (9, 16, 274, 302, 307–314) and TBI models (315–317). A typical approach has been to use multivariate pattern detectors such as principal component analysis (PCA) to distill numerous measurement variables down to a small number of multivariate patterns. PCA (318) and related approaches such as exploratory factor analysis (303) are classical tools for detecting the common variance that is shared by multiple observed variables. This represents a powerful approach to consolidate data in a hypothesis-free manner to discover the underlying associations among measures. This may be especially useful in disease models such as SCI and TBI wherein researchers often have only vague notions that several outcomes might be related. For example, gray matter sparing, white matter sparing, and locomotor performance may move together as a group; however, there may not be strong hypotheses about the magnitude or multi-dimensional/multi-inflected nature of that relationship (92, 241). It is conceivable that early functional performance could reflect gray matter sparing through early neuroprotection whereas later performance is predicted by an amalgamation of gray matter sparing as well as white matter sparing and remyelination (49, 69, 319, 320). Multivariate pattern detectors provide an unbiased way to identify these relationships in a manner that is untarnished by preconceptions (e.g., hypotheses) about how the data should look.

Once identified, multivariate patterns can be used as outcomes for statistical hypothesis testing. For example, Grau et al. (2004) used PCA to deal with multiple outcomes in a spinal contusion model (302). Numerous histological and behavioral variables were distilled using PCA to identify data-driven outcome clustering. In a second step, hypothesized group differences were tested using multivariate analysis of variance and linear discriminant function analysis. By testing for consensus between alternative approaches of data-driven and hypothesis-driven statistics, the authors were able to make strong arguments about multivariate patterns that were highly robust. Others, such as Courtine et al. (2009), used PCA to detect clustering of 135 kinematic variables into systematic patterns during recovery after spinal cord transection (307). These patterns were then used (in the form of PC scores) to test for therapeutic interventions, revealing therapeutics that affected a large number of outcomes as a coherent pattern. This can be thought of as a data-filtering approach that uses *all* of the information within

the dataset as a preamble to hypothesis testing. In this way, the hypothesized therapeutic approach can be tested on the entire ensemble of outcomes through syndromic analysis.

In some neurotrauma datasets, however, the multivariate association among measures is an end in itself. For example, a recent paper was concerned with whether a novel morphological observation—extensive corticospinal tract sprouting in primates after SCI—was related to functional performance (16). Fortunately, this group took multiple functional measures from the same animals (214, 226), enabling a syndromic analytical approach. Through rigorous measurement of multiple variables from EMG, kinematics, observational scales and tissue morphology, and matched efforts in data organization/data annotation, it was possible to perform syndromic analysis, revealing the multivariate association between the degree of CST sprouting and functional performance. This highlights the powerful opportunity for novel discoveries that can come from syndromic analysis, if neurotrauma researchers can develop well-organized multivariable datasets.

Validation of Syndromic Patterns

Once multivariate syndromic patterns are extracted, their validity and reliability can be assessed through a number of statistical and experimental approaches. For example, statistical perturbation analyses can be used to subsample subject populations (bootstrapping) or variable sets (feature selection) to evaluate the generality of syndromic patterns across diverse data types. An exhaustive review of such "model selection approaches" is beyond the scope of the present paper, and we refer readers to excellent outside sources (321). Multivariate approaches have been widely exploited to validate genomic patterns as predictors of a particular disease state (322). Preclinical neurotrauma research has powerful additional opportunity for syndromic validation beyond just statistical approaches. Trauma, unlike many other neurological diseases, has a known etiology that can be precisely replicated in the laboratory using controlled biomechanical injury devices (323–325). Syndromic patterns can be validated by their sensitivity to biomechanically defined injury gradations. This fundamental fact—that the basic etiology of neurotrauma is known—uniquely positions the neurotrauma literature to help tune translational syndromic methods for potential applications to other neurological diseases that do not benefit from a well-characterized etiology.

Achieving High N through Data Sharing

One of the hurdles for syndromic testing is that the typical sample size (N) used in basic neurotrauma experiments is

much smaller than traditionally thought to be required for multivariate statistical studies. Historically, multivariate statistical approaches, such as exploratory factor analysis and principal components analysis, were held to require sample sizes of $N>250$ for reliable detection of multivariate patterns (304). This traditional rule of thumb for sample size presents a challenge for syndromic analysis in neurotrauma models because it is a far greater N than a typical basic research laboratory is able to achieve in a single study. However, recent Monte Carlo studies have suggested that multivariate methods can be reliably applied when certain statistical criteria are met (high communalities and high levels of component saturation) (326). These statistical features are often met in basic neurotrauma research because animal models are well-standardized, resulting in reduced error variance and better resolution at the multivariate level (327). In addition, the bioinformatics field has produced a number of new statistical methods, such as sparse principal components analysis, that are less vulnerable to distortions of multivariate patterns created by low Ns (328). Together, recent innovations in the statistical literature provide support for the application of multivariate approaches to 'low-N' basic neurotrauma research, as long as researchers apply the appropriate statistical safeguards (e.g., sparse PCA with the L_1 penalty (329)).

Although there are no technical difficulties with applying modern multivariate methods to small datasets, there is still a strong argument for developing large, shared datasets to improve translation of multivariate findings. By applying multivariate pattern detection on large-scale heterogeneous datasets, it becomes possible to identify emergent multivariate patterns that translate across diverse laboratories and models (175). The goal of taking such an approach is to identify consistent syndromic patterns that reflect translational measures of neurotrauma pathology (176) and therefore consistent targets for translational testing.

Common Data Elements for Preclinical Animal Models

Identification of candidate common data elements (CDEs) for basic animal research will be critical for the success of data-sharing efforts and syndromic analysis (175, 176). CDEs are variables that have well-defined operational definitions and use the same variable names across different studies. Under the direction of the National Institute of Neurological Diseases and Stroke (NINDS), the clinical neurotrauma literature has undertaken a substantial effort toward developing CDEs for clinical trials for both TBI (306, 330–334) and SCI (209). At the current time, the preclinical literature has lagged behind the clinical literature in identifying CDEs for translational testing, and there is a lack of consensus in the field as to the best methods to

move forward (28, 29). Collaborative data-sharing across multiple laboratories has the potential to assist in this effort. With the exception of the MASCIS trial from the early 1990s (266), there are few examples of large-scale data-sharing projects in the preclinical literature. We have recently undertaken a large-scale data-sharing effort involving several SCI research centers including UCSF, UCSD, UCLA, UCI, University of Louisville, and the Ohio State University (175, 176). The goal of this project is to develop a common database infrastructure for animal SCI research that will enable large-scale syndromic discovery and translation between species (Fig. 4).

Syndromics as a Generalizable Framework for Multiple Diseases

At the current time, most of the syndromic work for neurotrauma has been isolated to a small number of high-profile papers (16). However, we anticipate that syndromic approaches will begin to become prevalent in a wide variety of disease models. The goal is to monitor and capture as much information as possible about the state of the subject and then use advanced analytical techniques to leverage this information in the process of therapeutic testing. The syndromic approach represents a stark contrast from historical methods used in preclinical outcome research, which have relied heavily on pre-existing hypotheses and strong theoretical foundations. While hypothesis-driven research is a powerful approach for proof-of-concept testing in highly controlled experimental scenarios, it may not be the best method for detecting translational therapeutic effects in complex systems such as the injured nervous system in vivo (253–257).
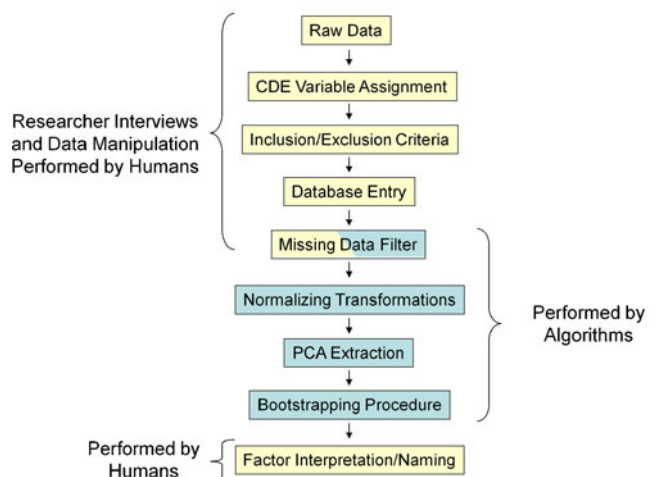

Fig. 4 Methodological workflow for syndromic analysis

The clinical literature has long acknowledged the problem of complexity, and there would be substantial translational power gained by adopting similar analytic methods in the basic scientific research. Indeed, factor analysis, one of the first multivariate techniques, was developed to tackle the problem of complexity in human cognitive testing (303). These methods were later extended to a wide variety of clinical problems including human diagnostics such as intelligence tests (303, 335), neuro-cognitive inventories (336), electrocardiograms (337, 338), pain measures after SCI (339), and the AIS scale (340) and will greatly benefit our efforts in the preclinical models.

Concluding Remarks

In this review, we presented syndromics as a new framework for dealing with data from basic neurotrauma research. The goal of syndromics is to leverage existing knowledge within the vast basic science literature to discover new patterns within disease models. This approach is consistent with innovations in analytical methods for systematic reviews (341) and meta-analyses (342–344) in the sense that it combines findings from several sources to characterize the emergent trends within a field of study. However, unlike traditional meta-analyses of data that is extracted from published works, syndromic analysis involves access to the original raw data from diverse scales and relies heavily on open data-sharing among researchers (345). In recent years, the genomic field has pioneered data-sharing standards which have enabled new meta-analytic techniques such as gene-set enrichment analysis (GSEA) and on raw data in genomic databases or meta-GSEA which combines multi-center data after correcting for variance in gene expression across studies (322, 346–348). However, at the current stage, there is little intrinsic incentive for preclinical neurotrauma researchers to engage in a similar data-sharing exercise using diverse histological and functional outcome sets for syndromic analysis. The NIH has a resource sharing policy that demands timely release and access to data upon request by other researchers for data collected as part of an NIH project (349). However, as previously pointed out (345), getting data to the point that it can be shared often requires substantial effort, and it is unclear who should shoulder this burden. It is understandable that researchers who have ongoing obligations to new projects will have little time/resources available to help index their old data, especially when data are collected by graduate students, postdocs, and other research staff who were not trained in standards for that file structures, variable names, and large-scale quantification methodologies.

Because multivariate techniques, such as those advocated in this review, are not yet common in the basic neurotrauma literature, the field has an opportunity to develop consensus-based standards for collection of multivariate basic neuro-trauma data. In the immediate future, the field would benefit from the implementation of multivariate techniques to assess the redundancy of the current measures of function. This would streamline the current testing methods, allowing for a more organized literature. In the more distant future, the field could harness multivariate techniques to better assess the validity of new measures. In addition to methodological gains, researchers could use advanced statistical techniques such as structural equation modeling (e.g., Fig. 3b) to produce theoretical gains as well. Therefore, future work that leverages these methodologies is likely to be informative and applicable to multiple fields of study.

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